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REVIEW ARTICLE

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Does Time to Achieve a Targeted Body Temperature Matter for Survivors of Cardiac Arrest? A Systematic Review and Meta-Analysis

Khalid S. Alotaibi, MSc[1,2]
Naveed Saleem, MSc, MD[1]
Timothy Arthur Chandos Snow, PhD[1]
Pietro Arina, PhD[1]
Alex Dyson, PhD[1,3]
Mervyn Singer, MD, FRCP[1]

OBJECTIVES: To identify the impact of early hypothermic temperature control (HTC) initiation and achievement on neurologic outcomes after cardiac arrest. Secondary endpoints assessed: 1) overall survival, 2) body temperature at hospital admission, 3) time taken to reach targeted temperature, and 4) adverse events. Subgroup analyses assessed: 1) HTC induction method, 2) presenting rhythms (shockable vs. nonshockable), and 3) timing of HTC initiation (during cardiopulmonary resuscitation [CPR] vs. post-return of spontaneous circulation [ROSC]).

DATA SOURCES: PubMed, Cochrane Library, U.S. National Library of Medicine, MedRxiv, BioRxiv.

STUDY SELECTION: Prospective randomized controlled trials enrolling comatose adult cardiac arrest patients that assessed the efficacy of early cooling (defined by initiation of HTC within 30 min of ROSC) against late cooling.

DATA EXTRACTION: Two reviewers independently conducted study selection, data extraction, and assessment of evidence quality. Full texts were jointly reviewed, with discrepancies resolved by a third reviewer through discussion and consensus.

DATA SYNTHESIS: Of 7269 citations, 11 met the inclusion criteria. Early cooling did not improve neurologic outcomes (risk ratio [RR], 1.01; 95% CI, 0.94–1.14) nor survival (RR, 1.01; 95% CI, 0.92–1.11). Nasal evaporative cooling initiated during resuscitation may benefit patients with shockable rhythms (RR, 1.40; 95% CI, 1.00–1.96), while administering cold fluid during CPR was associated with a higher risk of rearrest. Cooling was initiated in the prehospital phase in ten studies, nine of which failed to achieve target temperature (32–34°C) by hospital admission. The median time to reach target temperature ranged from 38 to 360 minutes.

CONCLUSIONS: Early HTC showed no neurologic nor survival benefit in cardiac arrest survivors. Nasal evaporative cooling during CPR may benefit those with shockable rhythms. Delays in reaching the target temperature may underlie the failure of HTC. Future studies should evaluate whether achieving target temperature, for example, within 30 minutes, rapidly improves outcomes.

KEYWORDS: cardiac arrest; early temperature control; hypothermic temperature control; neurologic function; oxidative stress; survival

Cardiac arrest (CA) represents the extreme of critical illness and still carries a poor prognosis. Out-of-hospital CA (OHCA), occurring in ~55 per 100,000 people annually, accounts for most cases (1). Despite advances in the "chain of survival" (early recognition, bystander

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KEY POINTS

Question: Hypothermic temperature control (HTC) was formerly recommended after cardiac arrest to reduce brain metabolism and production of reactive oxygen species (ROS) during the reperfusion phase. Given the lack of clinical benefit observed in large randomized controlled trials where targeted temperature was reached late, does the early initiation of HTC, and rapid achievement of target temperature, improve neurologic outcomes and overall survival in cardiac arrest survivors?

Findings: Early HTC did not improve neurologic function nor overall survival. Notably, where reported, all studies failed to achieve the target temperature range (32–34°C) within 30 minutes when ROS production would be highest.

Meaning: HTC is no longer recommended in survivors of cardiac arrest. The failure of HTC studies may, however, relate to delayed attainment of target temperature and likely missing the therapeutic window. A more aggressive HTC protocol should be investigated.

cardiopulmonary resuscitation [CPR], and early defibrillation), neurologic impairment remains common among survivors. Only ~10% survive to hospital discharge, often with lasting brain injury (1, 2). The impact of OHCA on quality and quantity of life remains a major societal and healthcare burden (3–6).

Hypothermic temperature control (HTC) is now the preferred nomenclature for what was previously termed "therapeutic hypothermia" or "targeted temperature management" (TTM) (7–10). HTC management strategies involve lowering and maintaining core temperature at 32–34°C in comatose CA patients (7–9). By downregulating cerebral metabolism, HTC is considered to reduce mitochondrial electron chain activity and thus reactive oxygen species (ROS) production, thereby preserving neurologic function through prevention of oxidative damage (11–13). HTC was formerly routine clinical practice (7–9); however, two large multicenter studies (TTM-1 and TTM-2) (14, 15) failed to demonstrate any outcome benefit. Guideline recommendations changed from cooling to hypothermic levels to preventing hyperthermia (defined as a core temperature > 37.7°C) for 72 hours post-CA (10).

Preclinical models indicate that HTC is only effective when initiated early, ideally commencing during resuscitation (16–18). In a canine study, brain injury was reduced when temperature was lowered to 34°C within 30 minutes post-return of spontaneous circulation (ROSC), with the greatest benefit seen when cooling began during CPR (17). By contrast, the TTM-1 and TTM-2 patient trials did not achieve target temperatures until a median 6–8 hours after arrest (14, 15). This delay likely exceeds the optimal therapeutic window for HTC, perhaps accounting for the lack of benefit.

As ROS are generated within minutes of reperfusion (i.e., during CPR or immediately after ROSC) (19), and preclinical data support the use of early HTC, we hypothesized that early initiation of HTC (within 30 min of ROSC) (17) would improve survival in patients with better neurologic outcomes. We therefore conducted a systematic review and meta-analysis of randomized trials involving HTC in comatose CA patients. Subgroup analyses explored the influence of HTC induction methods, timing (during vs. after CPR), presenting rhythm (shockable vs. nonshockable), and time to achieve target temperature on clinical outcomes.

MATERIALS AND METHODS

This systematic review and meta-analysis was registered with PROSPERO; registration number: CRD42024527328, and conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for randomized controlled trials (RCTs) (20).

Data Sources and Searches

A systematic search was performed in PubMed, Embase, Cochrane Library, U.S National Library of Medicine (ClinicalTrials.gov), MedRxiv, and BioRxiv using predefined terms (**Supplemental Table 1**, https://links.lww.com/CCM/H848). The search was last updated on February 20, 2025. Reference lists of relevant papers were screened for eligible studies.

Eligibility Criteria

We included prospective RCTs comparing early HTC (within 30 min of ROSC) to delayed HTC (after 30 min) (17). Studies involved in-hospital CA and OHCA patients with any initial rhythm (ventricular fibrillation [VF], pulseless ventricular tachycardia, pulseless

electrical activity, asystole) (**Supplemental Tables 2** and **3**, https://links.lww.com/CCM/H848). Only English-language papers describing studies enrolling comatose adults (≥ 16 yr) were included. No time constraints were employed.

Exclusion Criteria

Nonrandomized trials, pediatric studies, and non-English language papers without full-text translations were excluded. Studies involving traumatic CA were excluded. As were those comparing hypothermia with normothermia, rather than the timing of HTC.

Study Outcomes

The primary outcome was survival with good neurologic function, regardless of assessment method. Secondary outcomes included: 1) overall survival, 2) body temperature at hospital admission, 3) time required to reach target temperature range, and 4) complications related to HTC induction methods. Subgroup analyses examined: 1) HTC induction methods, 2) initial rhythm type (shockable vs. nonshockable), and 3) timing of HTC initiation (during CPR vs. post-ROSC).

Data Extraction and Analysis

Two reviewers (K.S.A., N.S.) independently screened titles and abstracts, followed by joint full-text assessment. Disagreements were resolved by a third reviewer (T.A.C.S.). Data extraction and statistical analyses were independently performed by the reviewers (K.S.A., N.S.), with cross-validation and discrepancies resolved by the reviewer (T.A.C.S.).

Meta-analyses were conducted using Review Manager Software (RevMan, version 5.4, Cochrane Collaboration, Oxford, United Kingdom). Forest plots were generated to visualize findings. Heterogeneity was assessed using the I^2 statistic, with thresholds of greater than 30%, greater than 50%, and greater than 75% indicating moderate, substantial, and considerable heterogeneity, respectively. A random-effects model with the Mantel-Haenszel method was used to evaluate the impact of early cooling on survival and neurologic outcomes. Statistical significance was set at p value of less than 0.05.

Trial sequential analysis (TSA) was conducted using TSA program (Version 0.9.5.10 Copenhagen Trial Unit) (www.ctu.dk/tsa) to account for potential type I errors in underpowered meta-analyses (21). This approach evaluates the reliability of the meta-analysis findings by integrating an estimate of the required information size (RIS), derived from the cumulative sample size of the included studies, with a statistically adjusted significance threshold. The analysis determined trial sequential monitoring boundaries (meta-analysis monitoring boundaries), RIS, diversity-adjusted information size (D2), and adjusted 95% CIs. The diversity adjustment was based on a predefined type I error rate of 5% and a statistical power of 80%. To demonstrate survival with good neurologic function comparing early vs. late initiation of HTC, RIS was calculated using a relative risk reduction (RRR) of 10%. As the TTM-1 and TTM-2 trials had been powered for 20% and 15% RRR, respectively, we opted for 10% given both trials were negative (14, 15).

Publication bias was assessed using a funnel plot, where the SE of each study's effect estimate was plotted against its corresponding effect size. Asymmetry was considered indicative of potential bias.

Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2 tool (22), which evaluates randomization, intervention adherence, missing data, outcome measurement, and selective reporting domains. Each domain was rated as "low," "high," or "some concerns." Two reviewers (K.S.A., N.S.) independently conducted assessments, with disagreements resolved through cross-validation and consensus with a third reviewer (T.A.C.S.).

Grading Quality of Evidence

Quality of evidence was assessed using the Grading of RecommendationsAssessment, Development, and Evaluation (GRADE) framework (GRADEpro, McMaster University, Hamilton, ON, Canada, 2015) (23), based on risk of bias, inconsistency, indirectness, imprecision, and other factors. Overall quality of evidence was rated as "very low," "low," "moderate," or "high."

RESULTS

Search Results

Our search identified 7269 citations (**Fig. 1**). After removing 109 duplicates and excluding 7121 based on title and abstract, 39 full texts were reviewed. Nine studies compared hypothermia to normothermia and

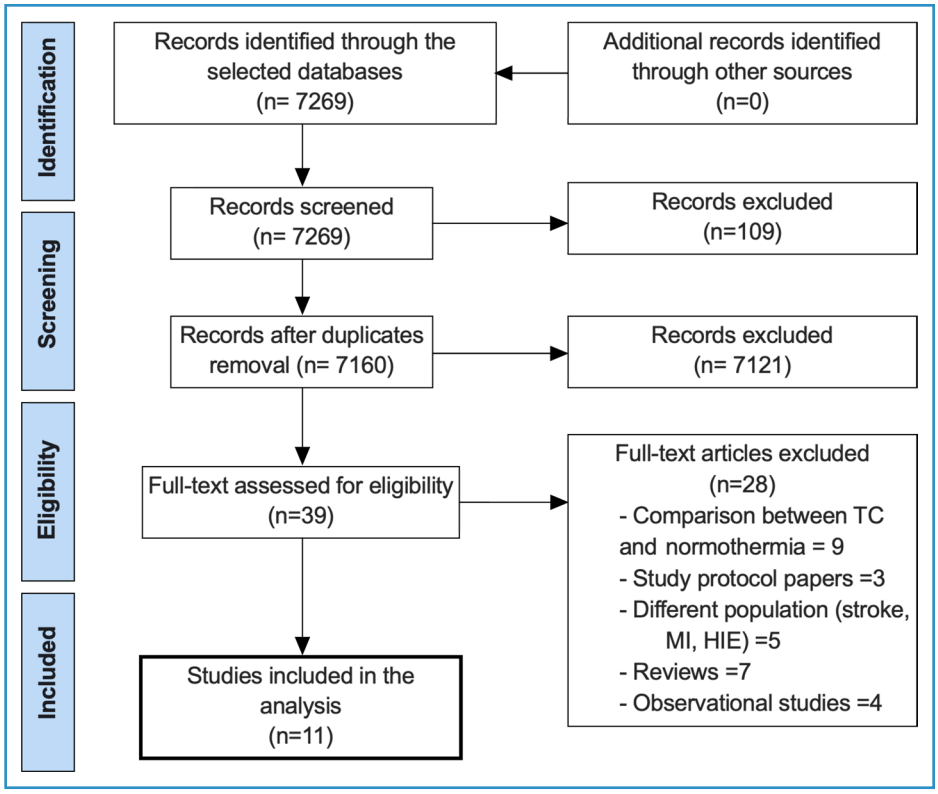
Identification
Screening
Eligibility
Included
Records identified through the selected databases (n= 7269)
Additional records identified through other sources (n=0)
Records screened (n= 7269)
Records excluded (n=109)
Records after duplicates removal (n= 7160)
Records excluded (n= 7121)
Full-text assessed for eligibility (n=39)
Full-text articles excluded (n=28)
- Comparison between TC and normothermia = 9
- Study protocol papers =3
- Different population (stroke, MI, HIE) =5
- Reviews =7
- Observational studies =4
Studies included in the analysis (n=11)

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. HIE = hypoxic-ischemic encephalopathy, MI = myocardial infarction, TC = temperature control.

five addressed other indications (e.g., stroke, myocardial infarction, hypoxic-ischemic encephalopathy). Additional exclusions included protocols, reviews, and observational studies. Eleven RCTs were included in the final analysis (24–34).

Characteristics of the Included Studies

The selected studies exhibited variations in individual characteristics (**Table 1**). Four were feasibility and safety trials (24, 25, 27, 31). Bernard et al (26) (2010) enrolled only patients with VF, while their 2012 trial focused on nonshockable rhythms (28). The remaining studies included patients with mixed rhythms. Most trials used IV cold fluids to induce cooling, while two employed transnasal evaporative cooling (27, 34). This technique delivers a coolant-oxygen mixture via the nasal cavity, which rapidly evaporates to reduce brain temperature. One feasibility study used a pharyngeal cooling device (31), similar to a supraglottic airway, with circulating cold saline within a closed system. Cooling was initiated in the prehospital setting in ten studies; only one began in hospital (31). Five studies started cooling during CPR, while six initiated cooling after ROSC.

Included studies defined good neurologic outcomes as patient being discharged (24, 29, 30), patient being discharged to either their home or to a rehabilitation center (26, 28, 32), patients achieving a Cerebral Performance Category (CPC) score of 1 or 2 (25, 27, 34), or a modified Rankin Scale (mRS) score of 0–2 (33). Additional details are shown in **Supplemental Table 4** (https://links.lww.com/CCM/H848).

Risk of Bias and Grading Level of Evidence

Eight of the 11 studies exhibited a high risk of bias (24–28, 30–32), with the remaining three raising some concerns (29, 33, 34). Double blinding was not feasible due to the nature of the interventions; the impact on adherence is unclear. Two studies lacked blinded outcome assessments (25, 27), while seven had no registered protocol or discrepancies between the protocol and article (24–26, 28, 30–32). Further details are provided in **Supplemental Table 5** (https://links.lww.com/CCM/H848). GRADE assessment found nonserious inconsistency for most outcomes, except for pulmonary edema. Indirectness and imprecision were not considered serious. The funnel plot showed symmetry, suggesting no publication bias, except for adverse event outcomes (**Supplemental Figs. 1–3**, https://links.lww.com/CCM/H848). Overall, quality of evidence was moderate for neurologic outcomes and survival, but low to very low for adverse events (**Supplemental Table 6**, https://links.lww.com/CCM/H848).

CLINICAL OUTCOMES

Neurologic Outcomes

Favorable neurologic outcomes were reported in ten studies including 4814 patients (2423 early cooling;

TABLE 1.
Characteristics of the Randomized Controlled Trials Comparing Early Versus Delayed Hypothermic Temperature Control After Cardiac Arrest

Study	Design	Sample	Presenting Rhythms	Study Arms	Cooling Method (Induction Phase)
Kim et al (24)	M-P-RCT	125	Mixed	Prehospital vs. hospital cooling	4°C n-saline
Kämäräinen et al (25)	Single-center-pilot randomized controlled trial	37	Mixed	Prehospital vs. hospital cooling	4°C RL
Bernard et al (26)	S-RCT	234	Ventricular fibrillation	Prehospital vs. hospital cooling	Cold RL
Castrén et al (27)	M-P-RCT	200	Mixed	Intra-arrest vs. hospital cooling	Transnasal evaporative
Bernard et al (28)	S-RCT	163	Nonshockable	Intra-arrest vs. hospital cooling	> 8°C Hartmann
Kim et al (29)	M-RCT	1359	Mixed	Prehospital vs. hospital cooling	4°C n-saline
Debaty et al (30)	M-RCT	245	Mixed	Intra-arrest vs. hospital cooling	> 8°C n-saline and surface cooling
Takeda et al (31)	M-P-RCT	113	Mixed	Intra- or post-return of spontaneous circulation vs. late cooling	Pharyngeal cooling
Bernard et al (32)	M-RCT	1198	Mixed	Intra-arrest vs. hospital cooling	3°C n-saline
Scales et al (33)	M-RCT	585	Mixed	Prehospital vs. hospital cooling	4°C n-saline, ice packs
Nordberg et al (34)	M-RCT	677	Mixed	Intra-arrest vs. hospital cooling	Transnasal evaporative

Mixed = shockable and nonshockable rhythms, M-P-RCT = multicenter-pilot randomized controlled trial, M-RCT = multicenter-randomized controlled trial, RL = Ringer's lactate, S-RCT = single-center randomized controlled trial.
Early cooling was defined if intervention was initiated within 30 min from achieving return of spontaneous circulation; late cooling started after 30 min.

2391 late cooling). No difference was observed between groups (risk ratio [RR], 1.03; 95% CI, 0.94–1.14; TSA-adjusted CI, 0.88–1.22) (**Fig. 2**). Favorable neurologic outcomes were observed in 543 and 514 patients in the early and late cooling groups, respectively. Results remained consistent regardless of intervention timing or cooling method (**Supplemental Figs. 4** and **5**, https://links.lww.com/CCM/H848). Notably, patients with shockable rhythms undergoing nasal evaporative cooling during resuscitation showed improved neurologic outcomes, albeit just lacking statistical significance (RR, 1.40; 95% CI, 1.00–1.96; and Supplemental Fig. 5, https://links.lww.com/CCM/H848). No difference was seen in patients with nonshockable rhythms (**Supplemental Fig. 6**, https://links.lww.com/CCM/H848). Neither conventional nor TSA boundaries for benefit or harm were crossed; however, the boundary for futility was crossed with 44% of the RIS achieved (**Supplemental Fig. 7**, https://links.lww.com/CCM/H848).

Survival

Survival outcomes were reported in 4922 patients (2476 early cooling; 2446 late cooling). No difference was found between groups (RR, 1.01; 95% CI, 0.92–1.11; TSA-adjusted CI, 0.88–1.16; **Fig. 3**). Subgroup analyses showed consistent survival regardless of cooling method, timing, or cardiac rhythm (**Supplemental Figs. 8–10**, https://links.lww.com/CCM/H848). Neither conventional nor TSA boundaries for benefit or harm were crossed. The boundary for futility was crossed with 52% of RIS achieved.

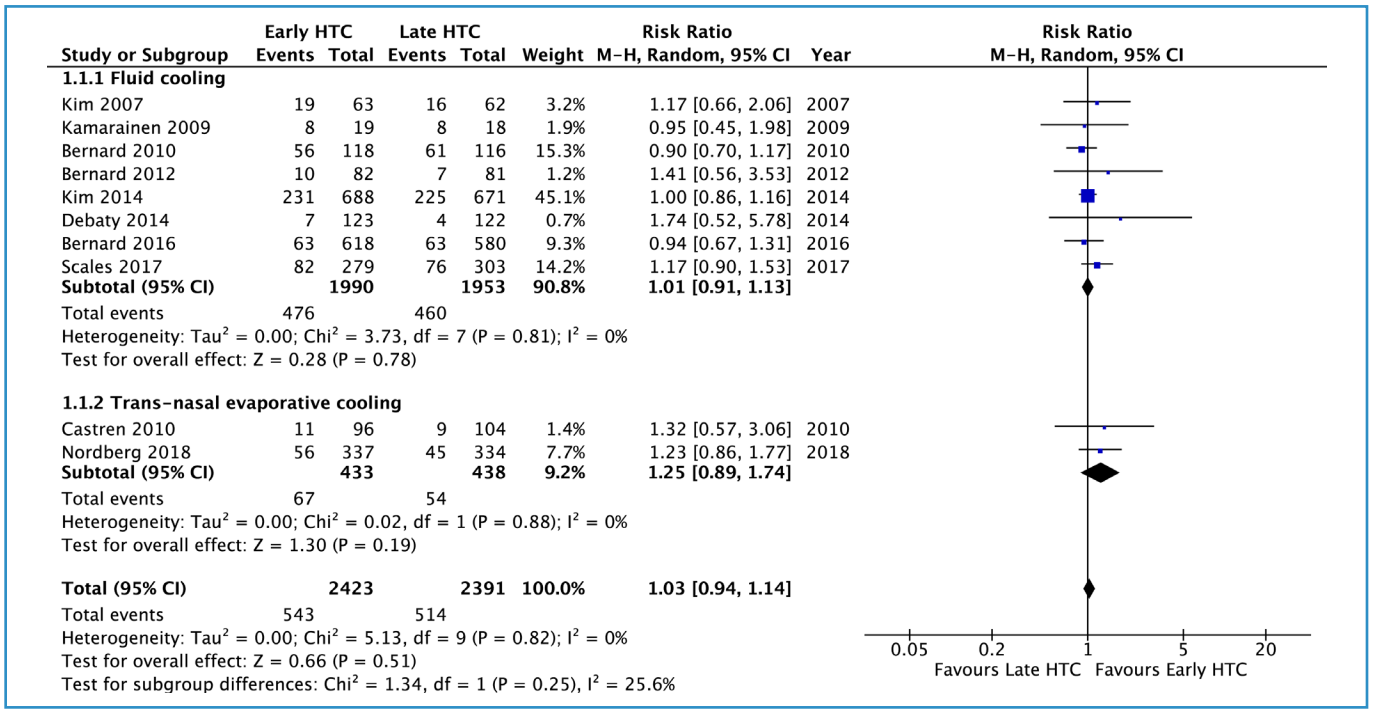
Early HTC
Late HTC
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
1.1.1 Fluid cooling
Kim 2007 19 63 16 62 3.2% 1.17 [0.66, 2.06] 2007
Kamarainen 2009 8 19 8 18 1.9% 0.95 [0.45, 1.98] 2009
Bernard 2010 56 118 61 116 15.3% 0.90 [0.70, 1.17] 2010
Bernard 2012 10 82 7 81 1.2% 1.41 [0.56, 3.53] 2012
Kim 2014 231 688 225 671 45.1% 1.00 [0.86, 1.16] 2014
Debaty 2014 7 123 4 122 0.7% 1.74 [0.52, 5.78] 2014
Bernard 2016 63 618 63 580 9.3% 0.94 [0.67, 1.31] 2016
Scales 2017 82 279 76 303 14.2% 1.17 [0.90, 1.53] 2017
Subtotal (95% CI) 1990 1953 90.8% 1.01 [0.91, 1.13]
Total events 476 460
Heterogeneity: Tau² = 0.00; Chi² = 3.73, df = 7 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)
1.1.2 Trans-nasal evaporative cooling
Castren 2010 11 96 9 104 1.4% 1.32 [0.57, 3.06] 2010
Nordberg 2018 56 337 45 334 7.7% 1.23 [0.86, 1.77] 2018
Subtotal (95% CI) 433 438 9.2% 1.25 [0.89, 1.74]
Total events 67 54
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)
Total (95% CI) 2423 2391 100.0% 1.03 [0.94, 1.14]
Total events 543 514
Heterogeneity: Tau² = 0.00; Chi² = 5.13, df = 9 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Chi² = 1.34, df = 1 (P = 0.25), I² = 25.6%
0.05 0.2 1 5 20
Favours Late HTC Favours Early HTC

Figure 2. Random-effect meta-analysis comparing the impact of early vs. late hypothermic temperature control (HTC) on good neurologic outcomes following cardiac arrest. *df* = degrees of freedom, M-H = Mantel-Haenszel.

Body Temperature at Hospital Admission and Time to Reach Targeted Temperature

In ten studies, prehospital cooling reduced core temperature by hospital admission but failed to achieve the guideline-recommended target of 32–34°C (**Table 2**). Median time to reach the target temperature range ranged from 38 to 360 minutes. (Table 2). Both conventional and TSA boundaries for benefit were crossed, indicating that the RIS had been achieved.

MEDICAL COMPLICATIONS

Pulmonary Edema and Rearrest

Pulmonary edema was commonly reported, particularly with the use of cold IV fluid (29, 32). No difference was found between early and delayed cooling groups (RR, 1.12; 95% CI, 0.71–1.75; **Fig. 4**). Since only four studies included this outcome, TSA could not be performed. Pulmonary edema rates were similar whether fluids were given during CPR or post-ROSC (**Supplemental Fig. 11**, https://links.lww.com/CCM/H848). Rearrest rates were more frequent in patients cooled with cold fluids (RR, 1.19; 95% CI, 1.00–1.42; TSA-adjusted CI, 0.58–2.4) (Fig. 4). Neither conventional boundary, nor the TSA boundaries for benefit/harm or futility were crossed, with 13% of RIS achieved.

Nasal Bleeding and Discoloration

Transnasal evaporative cooling was associated with increased nasal bleeding (RR, 18.20; 95% CI, 2.39–138.39) and nasal discoloration (RR, 15.95; 95% CI, 2.11–120.47; Fig. 4). Only two studies reported this outcome thus TSA could not be performed.

DISCUSSION

In this systematic review and meta-analysis, we evaluated whether early initiation of HTC, defined as initiation during CPR or within 30 minutes of ROSC, improved neurologic outcomes and overall survival. No differences were seen in outcomes between early and late initiation cooling. Although HTC was initiated during CPR in more than half of the included studies, the time to reach the target temperature range was protracted across all studies, with median times ranging from 38 to 360 minutes (Table 2). It also remains uncertain whether target temperatures were reliably achieved and maintained. Only two of the 11 studies reported these data and, even then, failed to

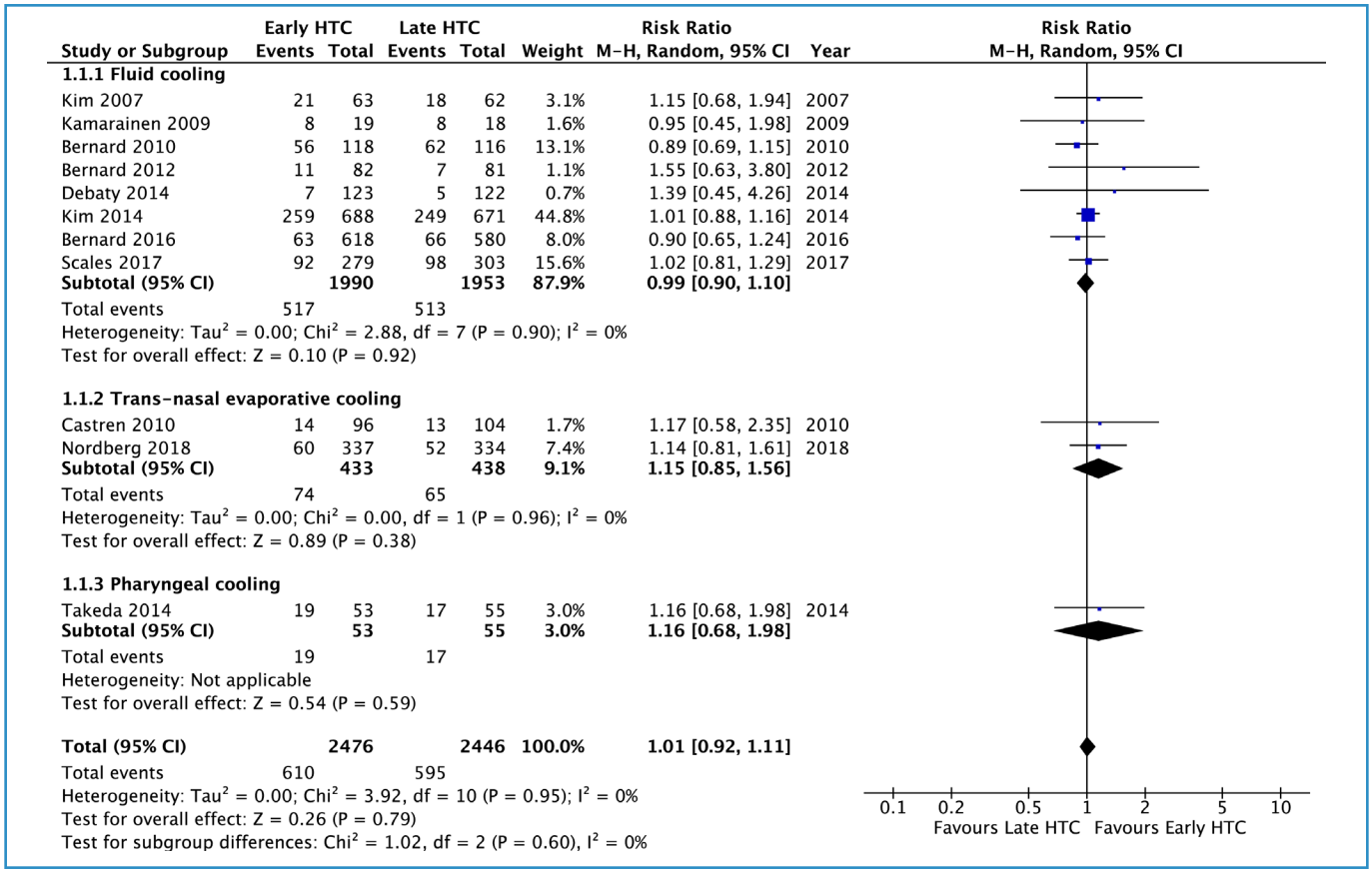
Early HTC
Late HTC
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
1.1.1 Fluid cooling
Kim 2007 21 63 18 62 3.1% 1.15 [0.68, 1.94] 2007
Kamarainen 2009 8 19 8 18 1.6% 0.95 [0.45, 1.98] 2009
Bernard 2010 56 118 62 116 13.1% 0.89 [0.69, 1.15] 2010
Bernard 2012 11 82 7 81 1.1% 1.55 [0.63, 3.80] 2012
Debaty 2014 7 123 5 122 0.7% 1.39 [0.45, 4.26] 2014
Kim 2014 259 688 249 671 44.8% 1.01 [0.88, 1.16] 2014
Bernard 2016 63 618 66 580 8.0% 0.90 [0.65, 1.24] 2016
Scales 2017 92 279 98 303 15.6% 1.02 [0.81, 1.29] 2017
Subtotal (95% CI) 1990 1953 87.9% 0.99 [0.90, 1.10]
Total events 517 513
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 7 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
1.1.2 Trans-nasal evaporative cooling
Castren 2010 14 96 13 104 1.7% 1.17 [0.58, 2.35] 2010
Nordberg 2018 60 337 52 334 7.4% 1.14 [0.81, 1.61] 2018
Subtotal (95% CI) 433 438 9.1% 1.15 [0.85, 1.56]
Total events 74 65
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.38)
1.1.3 Pharyngeal cooling
Takeda 2014 19 53 17 55 3.0% 1.16 [0.68, 1.98] 2014
Subtotal (95% CI) 53 55 3.0% 1.16 [0.68, 1.98]
Total events 19 17
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)
Total (95% CI) 2476 2446 100.0% 1.01 [0.92, 1.11]
Total events 610 595
Heterogeneity: Tau² = 0.00; Chi² = 3.92, df = 10 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Chi² = 1.02, df = 2 (P = 0.60), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favours Late HTC Favours Early HTC

Figure 3. Random-effect meta-analyses comparing the impact of early against late hypothermic temperature control (HTC) on overall survival after cardiac arrest. *df* = degrees of freedom, M-H = Mantel-Haenszel.

achieve the target temperature range in some patients (28, 29). The sparsity of data limits the extent to which this aspect can be critically analyzed.

The "ROS burst" associated with reperfusion occurs predominantly within the first few minutes following reperfusion (19, 35, 36). Assuming HTC is an effective therapy, the obvious corollary is that earlier cooling to a target temperature would improve outcomes. Supporting this, a pioneering canine study of VF arrest demonstrated improved brain histology in animals cooled to 34°C within 30 ± 1 minutes following reperfusion (17). Observational studies also indicate a superior impact from HTC when initiated shortly after CA (37). The optimal therapeutic window in humans remains to be delineated.

Early cooling within 30 minutes of ROSC did achieve a reduction in body temperature upon hospital admission, but none achieved the recommended depth (32–34°C). Only two studies achieved target temperature within 1 hour, highlighting the inefficiency of the methods used to lower body temperature rapidly. Of note, the predominant method for recording body temperature at hospital admission was tympanic, although this screening method does not accurately reflect brain nor core temperature (38–41).

Notwithstanding notable advancements in cooling technology (27, 42–44), prehospital induction of HTC relies primarily on administration of large volumes of crystalloids, despite guidelines discouraging this approach (9, 10). Use of cold fluid was associated with an increased occurrence of pulmonary edema, a higher rate of rearrest, and a lower likelihood of achieving ROSC (29, 32). Volumes of cold fluid administered ranged from 640 to 2000 mL, with the occurrence of pulmonary edema increasing at higher volumes (29, 33). A higher occurrence of pulmonary edema was also seen in the early cooling arm when cold fluid was administered; however, this was not statistically significant despite a higher occurrence of rearrest. This discrepancy may be attributed to potential misdiagnosis of pulmonary edema, as it may not be manifest during resuscitation or at hospital admission. The administration of large fluid volumes may also increase central venous pressure, which, in turn, may reduce coronary

TABLE 2.
Temperature at Hospital Admission, Measurement Methods, and Time to Reach Targeted Temperature

Study	Interventions	Temperature at Admission, Celsius, Mean ± SD	Method Used to Record Temperature	Time to Reach Targeted Temperature (min), Median (IQR)
Kim et al (24)	Early HTC vs. late HTC	34.7 ± 1.2 vs. 35.7 ± 1.2	Esophageal	NR
Kämäräinen et al (25)	Early HTC vs. late HTC	34.1 ± 0.9 vs. 35.2 ± 0.8	Nasopharyngeal	60 (NR) vs. NR
Bernard et al (26)	Early HTC vs. late HTC	34.6 ± 1.3 vs. 35.4 ± 1	Tympanic	360 (NR) vs. 540 (NR)
Castrén et al (27)	Early HTC vs. late HTC	34.2 ± 1.5 vs. 35.5 ± 0.9	Tympanic	155 (124–315) vs. 284 (172–315)
Bernard et al (28)	Early HTC vs. late HTC	34.4 ± 1 vs. 35.7 ± 1	Tympanic	192 (NR) vs. 288 (NR)
Kim et al (29)	Early HTC vs. late HTC	34.9 ± 1.7 vs. 35.8 ± 0.8	Tympanic/ esophageal	252 (NR) vs. 330 (NR)
Debaty et al (30)	Early HTC vs. late HTC	33.9 ± 1.4 vs. 35 ± 1	Esophageal	38 (NR) vs. 105 (NR)
Takeda et al (31)	Early HTC vs. late HTC	33.7 ± 1.4 vs. 34.1 ± 1.1*	Tympanic	151 (NR) vs. NR
Bernard et al (32)	Early HTC vs. late HTC	34.7 ± 1.2 vs. 35.4 ± 1.3	Tympanic	NR
Scales et al (33)	Early HTC vs. late HTC	35.1 ± 1 vs. 35.2 ± 1.7	NR	324 (180–492 vs. 288 (168–462)
Nordberg et al (34)	Early HTC vs. late HTC	34.8 ± 0.9 vs. 35.7 ± 0.3	Tympanic	105 (80–178) vs. 182 (132–312)

HTC = hypothermic temperature control, IQR = interquartile range, NR = not reported.
Early HTC was defined if intervention was initiated within 30 min from achieving return of spontaneous circulation; late cooling started after 30 min. The study by Takeda et al (31) initiated cooling in-hospital and temperature was recorded after 40 min.

perfusion pressure (45). Experimental data suggests that fluid-based HTC is most beneficial when applied without excessive volume loading (45). Other adverse event reporting, such as electrolyte disturbances or coagulopathy, was sparse.

A more recent approach to selective brain cooling is the transnasal evaporative technique. Both reporting studies employed this technique only for the initial 2 hours to initiate HTC, following which systemic cooling was applied (27, 34). This approach resulted in minor nasal bleeding in 24 patients and severe bleeding in a few cases, thus necessitating termination of the procedure (27, 34). By contrast to systemic cooling, selective brain cooling offers the advantage of fewer complications such as shivering, arrhythmia, and immunosuppression (15, 46, 47). Encouragingly, in a pig model using vortex tubes as mechanical devices to produce cold air, the brain could be cooled at a rate of 4°C per hour (48).

Our subgroup analyses suggest a potential therapeutic benefit in patients with shockable rhythms, particularly when HTC was initiated during resuscitation via nasal evaporative cooling, the limited sample size in this subgroup analysis may have resulted in a finding that did not reach the predefined statistical threshold. An ongoing multicenter RCT is currently reevaluating the effectiveness of HTC in this patient population (49). Another ongoing study is enrolling patients irrespective of their presenting cardiac rhythm, aiming to achieve a core body temperature of 33.0 ± 0.5°C within 60 minutes of initiating cooling (50).

The included studies exhibit substantial heterogeneity in several key aspects, including depth and

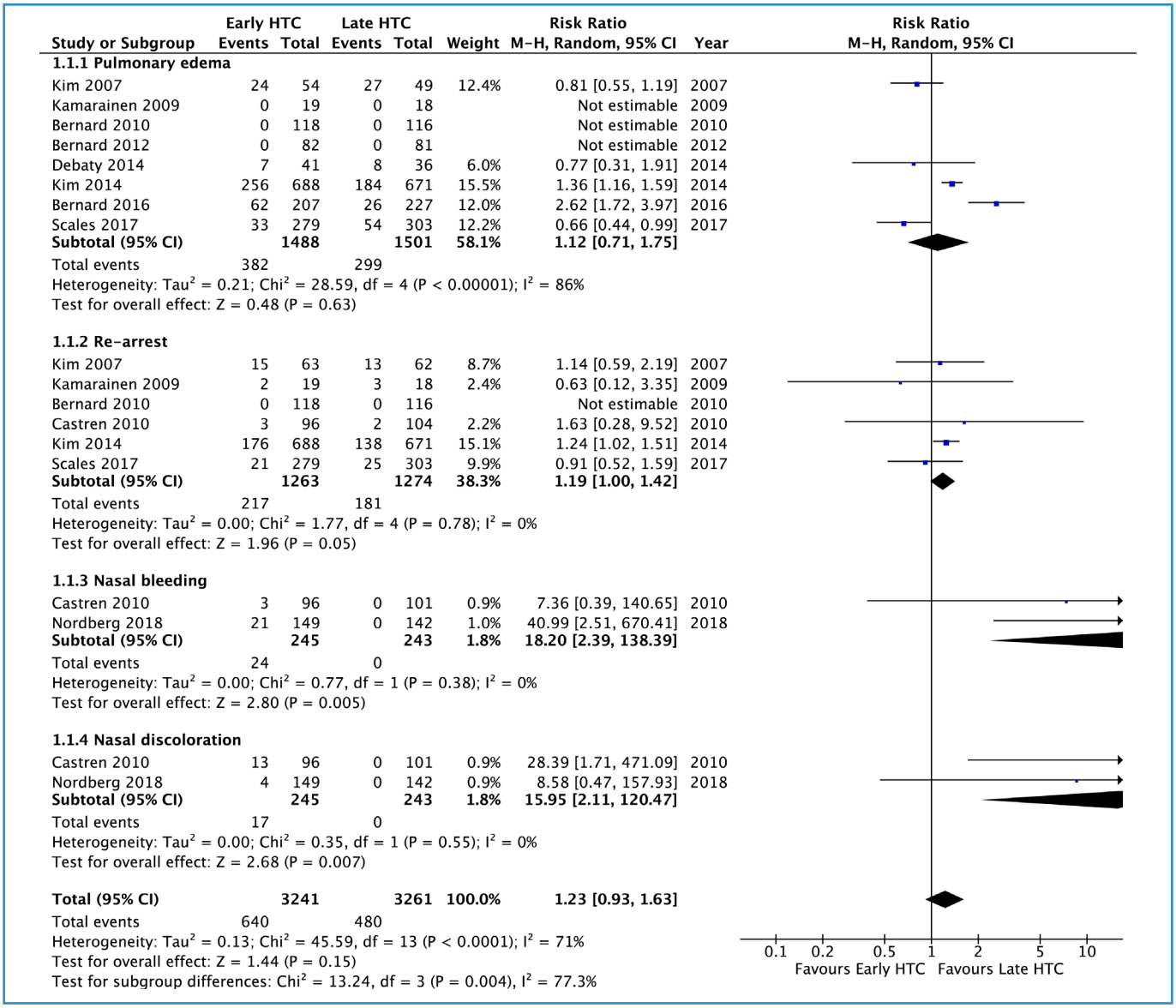

Figure 4. Random-effect meta-analyses of adverse events associated with the method used for induction of hypothermic temperature control (HTC). *df* = degrees of freedom, M-H = Mantel-Haenszel.

duration of cooling, methods used for induction and maintenance, and the timing of implementation (intra-arrest vs. post-ROSC). One or more of these issues may have influenced study outcomes. Many studies also report deviations from protocols, instances where patients did not receive their assigned intervention (often due to prehospital transport times), and the presence of confounding factors such as variations in fluid administration (26) and co-administration of medications (e.g., paralytics and sedatives to prevent shivering).

Initiation of ROSC and, by consequence, reperfusion injury following CA leads to elevated oxidative stress with subsequent tissue and cell damage, and this contributes to poor clinical outcomes. Early cooling has yet to demonstrate any meaningful clinical benefit. This may be related in part due to complications that arise, but the protracted time to reach target temperatures should not be overlooked. A pharmacologic reduction in metabolism, as we have demonstrated in several preclinical studies using a sulfide donor, could be faster, easier, and potentially more effective compared with external cooling (51, 52). The utility of such approaches, either alone or combined with HTC, is worthy of further investigation.

Our study offers several novel findings. First, it provides an important update from a Cochrane analysis published in 2016 (53) that predates the three major

trials (32–34), which together contributed nearly half the patients included in our analysis. Second, rather than focusing on setting (prehospital vs. in-hospital), we evaluated timing of initiation, irrespective of location. Third, we assessed whether studies actually achieved the target temperature range, and how long it took to reach the target after initiation. This is a critical and often overlooked distinction; early initiation does not ensure HTC is effectively delivered. Fourth, we systematically assessed adverse events related to the methods used to induce early HTC. This is rarely addressed but, given the risks of aggressive cooling, is an important safety issue.

Our study also has several limitations. First, we defined early cooling as the initiation of HTC within 30 minutes of ROSC. However, the optimal therapeutic window for HTC, both in terms of timing and depth of cooling, remains to be clarified. Furthermore, the heterogeneity among our retrieved studies, coupled with small sample sizes in some trials, precludes the ability to draw definitive conclusions.

Our study protocol did not specify how neurologic outcomes should be assessed. More than half the included studies assessed good neurologic outcomes as the patient being discharged to home or a rehabilitation center, rather than using a specific scoring system. As none of the included studies assessed outcomes beyond 90 days, the impact on long-term neurologic recovery remains unknown. Even when neurologic scoring systems were used, variable time points were chosen. Expert consensus committees have recommended use of CPC or mRS (54) but should ideally state when survivors should be scored to improve consistency across studies. The impact of withdrawal of life-sustaining therapy, also not reported in the studies, could have confounded survival outcomes. Finally, variability in temperature measurement methods, specifically the inclusion of both core and noncore readings, may have introduced measurement bias and confounded the results.

CONCLUSIONS

These data showed no association between early HTC and improved outcomes after CA. Current methods for rapid HTC induction remain limited and are associated with potential adverse events. Further research should evaluate other alternatives, such as pharmacologic approaches that rapidly lower metabolism after ROSC, thereby reducing ROS overproduction and organ damage.

1 *Bloomsbury Institute of Intensive Care Medicine, Division of Medicine, University College London, London, United Kingdom.*

2 *King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia.*

3 *Centre for Pharmaceutical Medicine Research, Institute of Pharmaceutical Science, King's College, London, London, United Kingdom.*

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Mr. Alotaibi and Dr. Dyson conceptualized and designed the study. Mr. Alotaibi and Mr. Saleem developed the methodology, established the search strategy, and conducted the systematic search. Mr. Alotaibi, Mr. Saleem, and Dr. Chandos Snow analyzed and interpreted the data. Mr. Alotaibi drafted the initial article, and all authors contributed to revisions. Drs. Dyson and Singer supervised the study. Dr. Singer takes overall responsibility. All authors reviewed and approved the final article.

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For information regarding this article, E-mail: rmhalot@ucl.ac.uk

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The corresponding author can provide the data upon request.

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